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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,036	09/30/2002	Paul R. Sanberg	1372.623.PRCWOUS	5509

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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/009,036	SANBERG ET AL.	
	Examiner	Art Unit	
	DANIEL KOLKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,7,12-17 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,7,12-17 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks filed 14 November 2008 have been entered. No amendments were filed. Claims 1 – 2, 4, 7, 10, 12 – 17, and 19 are pending and under examination.

Maintained Rejections

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 – 2, 4, and 17 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Weiss (U.S. Patent 5,851,832) in view of Sanberg (1997. Soc. Neurosci Abstr 23(1-2):346, abstract 140.9) and Grabowski (1994. Exp Neurol. 127(1):126-136).

This rejection stands for the reasons previously made of record and explained in further detail below. Briefly, Weiss '832 patent teaches methods of treating diseases, including stroke, by administration of the progeny of human neural stem cells. See Weiss column 11 lines 5 – 18; column 3 first paragraph, column 64 lines 13 – 21. Applicant argues that Weiss teaches treatment of neurodegenerative diseases, which he considers to be separate from stroke, but fails to teach treatment of stroke. Applicant is respectfully directed to column 64 lines 12 – 22, which disclose that stroke is one of the conditions to be treated by administration of neural stem cells. See also column 63 line 63 – column 64 line 12. Although this section is entitled "Cardiac Arrest", it clearly details the results of an experiment which induced ischemia within the brains of rats. Carotid arteries were occluded and a hypovolemic state was induced (column 63 lines 64

– 66), hippocampal CA1 cells were damaged, which "is typical of damage observed in humans following cardiac arrest and the cause of severe memory and cognitive deficits" (column 64 lines 1 – 3). Neural stem cells were administered within the brain, and those cells were shown to differentiate into neurons (column 64 lines 3 – 12). Clearly Weiss teaches stroke can be treated by administering neural stem cells. Although the reference does not explicitly teach treatment of humans with stroke, Weiss indicates that the animal model used, inducing stroke in a rodent, recapitulates several of the important features of human ischemic stroke, suggesting to the artisan of ordinary skill that the method should not be limited to veterinary treatment of rats and perhaps other rodents, but that it should be extended to humans.

Applicant also argues that the reference by Weiss does not provide sufficient guidance to the number of cells that should be administered. The examiner concedes that the particular sections that discuss treatment of stroke do not explicitly indicate the number of cells that should be transplanted when stroke is treated. However, in other sections of the reference, Weiss teaches that 1 – 3 ul of cells at up 50 x 10^6 cells per ml were administered (see column 62 lines 15 – 40) to rats. This corresponds to up to 150,000 cells per animal. Assuming a weight of about 0.3 kg, this is a dose of 500,000 cells per kg of body weight. Weiss explicitly teaches using burr holes to provide entry to the skull (column 62 lines 30 – 40), which is in point to claim 2. However Weiss does not teach hNT neuronal cells, does not explicitly teach "a plurality of brain area sites", as recited in claims 1 and 17 and does not explicitly teach treatment of humans who have experienced stroke at least 3 hours prior to treatment, as recited in claim 1.

Sanberg teaches that hNT cells, transplanted into the brains of rats who had experienced ischemia-inducing surgery a month earlier, are effective to ameliorate behavioral symptoms of stroke. Sanberg teaches that of the doses tested (5,000 – 40,000 cells administered to adult rats), 40,000 cells was the most effective and 5,000 and 10,000 cells were not effective; 20,000 cells per rat was partly effective. Sanberg states that "[t]hese results provided further support to the notion that clonal cell lines (e.g. hNT cells) may be exploted to develop cellular therapies for CNS diseases" (final sentence of abstract), suggesting to the artisan of ordinary skill that the teachings might not just be limited to treatment of ischemic rats, but may include other species such as humans. The reference therefore is on point to treating stroke with hNT cells; however Sanberg does not explicitly teach administering the cells to humans and does not teach administration of at least 6 million cells, or a plurality of sites as

recited in claims 1 and 17. Further Sanberg does not explicitly teach using a burr to enter the brain as recited in claim 2 and does not teach administration of cells 3 months after the stroke as encompassed by claim 4.

Grabowski et al. teach another model of transplantation in which fetal cortex is grafted into the infarcted cortex of rats that having undergone middle cerebral artery occlusion 5-7 days, 3 weeks, or 8 weeks prior. The reference therefore is on point to treatment of stroke by administration of cells into the brains of affected patients. Grabowski teaches that when transplantation surgery is delayed, graft survival is significantly improved. These investigators conclude that a delay between lesion and transplantation is desirable in this stroke model. However Grabowski does not explicitly teach waiting at least 3 months as recited in claim 4, and does not teach hNT neuronal cells, does not explicitly teach "a plurality of brain area sites" as recited in claim 1.

It would have been obvious to one of ordinary skill in the art to modify the methods of Weiss, who teaches treatment of stroke by administering neural stem cells and indicates that such treatments will also be effective in humans, by substituting the hNT cells of Sanberg and by waiting at least 5-7 days, as taught by Grabowski. Additionally, it would have been obvious to one of ordinary skill in the art to use at least 6 million cells, given the teachings of both Weiss and Sandberg. The motivation to do modify the methods of Weiss would be to effectively treat stroke in humans. It would have been reasonable to expect success as well.

Applicant argues that 1) none of the references cited teach or render obvious the specific number of cells to be administered, and 2) an artisan of ordinary skill would not have had a reasonable expectation of success in treating humans, given that none of the cited prior art references show reduction to practice of treatment of humans and that there was poor success in extrapolating rodent-based studies to human therapies. Applicant's arguments have been fully considered but they are not persuasive.

With respect to the question of whether or not the references teach or suggest administration of "at least 6 million" cells, as required by independent claims 1 and 17, the examiner notes that both Weiss and Sanberg teach treatment of rats (Weiss, column 63 line 63 – column 64 line 21; Sanber, abstract). Rats weigh approximately 300 g, or 0.3 kg. Weiss teaches that administering up to 150,000 cells per animal is effective, and Sanberg teaches that 20,000 – 40,000 cells are effective. The range of effective cells corresponds to 66,666 to 500,000 cells per kg of body weight. Assuming a person weighs about 75 kg, if the dose were

scaled up based upon body weight, this would result in administration of 5,000,000 to 37,500,000 cells. Clearly the artisan of ordinary skill would have been motivated to select a point within this range as the most likely dose to be effective. Since most of the points within the range are above 6,000,000, and the dose shown by Sanberg to be maximally effective (40,000 cells per rat) corresponds to 10,000,000 cells per 75 kg human, the artisan of ordinary skill would have found selection of more than 6,000,000 cells obvious. Applicant discusses the differences between rat and mouse models of stroke, and how it might not be possible to directly scale up the number of cells on a body-weight basis. The discussion is not germane. Both Weiss and Sanberg treated rats (not mice) by implanting cells, and the teachings of Sanberg, who explicitly indicates that 40,000 cells were most effective when administered to rats, guides the artisan to select the relevant number of cells. Contrary to applicant's arguments, the prior art references themselves point the artisan of ordinary skill directly to the appropriate amount of cells.

With respect to the argument that there is not a sufficient correlation between the animal models presented in the prior art references cited and treatment of stroke in humans, the argument is unpersuasive. At the time the invention was made, inducing strokes in rodents was seen to be the best available animal model of human stroke. Weiss indicates that the model can recapitulate certain aspects of human stroke, including death of neurons within the hippocampus. Zhang 1997 (cited in office action mailed 14 August 2008) teaches that middle cerebral artery occlusion is a model for cerebral ischemia (stroke). The references cited in the previous office action indicate that some of the treatments which are effective in treating stroke in rodents are also effective in humans. Applicant argues that other references indicate that rodent stroke models are imperfect predictors of efficacious treatments of human stroke. Applicant cites a number of references in the remarks filed 14 November 2008, although it is noted that no copies of any references were provided for the examiner to inspect. Applicant cites Carmichael 2005 (NeuroRx 2:396-409), the examiner was able to obtain a copy of this reference and has included it in the present communication; although the reference was published after the effective filing date of the present application it appears to support the examiner's position that rodent models of stroke are generally acceptable in determining if a therapy is likely to be effective in treating human stroke. At p. 396, second paragraph Carmichael states that “[t]his review will deal with the specific aspects of human disease modeled in rodent stroke models of focal ischemic stroke… rodent models will continue to

provide the predominant basic science research into mechanisms of neural protection and neural repair after stroke... many standard rodent models are best suited to testing neuroprotective therapies." The reference goes on to review the scientific literature, and cites many references published prior to the effective filing date of this application indicating that rodent stroke models were generally accepted in the art. See for example p. 398 first complete paragraph – p. 402 second column, and the references cited in the table on p. 400.

Applicant also cites another post-filing reference, Kleim 2007 Institute for Laboratory Animal Research Journal 48(4):374-384, which the examiner was able to obtain. Again, while the reference is not prior art, it does indicate that rat models of stroke, such as those used by both Weiss and by Sanberg, are generally accepted in the field. See p. 374, section entitled "Advantages of Using Rat Models". The reference does point out certain limitations of the rat models (p. 375 first column), but generally the teachings are on point to the appropriate nature of the rodent MCA occlusion model. Note that at p. 375 final paragraph the reference cites articles dating back to the mid-1980s (over a decade before the earliest possible filing date of this application) as providing detailed instructions on how to perform the model. While the rodent models of stroke are imperfect, they do provide the artisan of ordinary skill with a reasonable expectation of success in identifying therapies to treat human stroke. This is evidenced by the large number of publications on these models, including many cited by Kleim which antedate the present application. It seems implausible that the large body of literature is directed only towards treatment of stroke in rats, and that the any studies trying to identify treatment of stroke in rats have no bearing on treatment of the same disease in humans.

The art of record indicates that rodent models of ischemia, including the experiments reported at p. 5 line 25 – p. 6 line 2 of the present specification, are an art-accepted model of stroke in humans. Since Sanberg explicitly teaches that hNT cells are effective in treating stroke in rats, and Weiss indicates that implantation of stem cells into humans will be effective in treating stroke, one of ordinary skill in the art would have had a reasonable expectation of success in treating human stroke. Thus the arguments that there would not have been such a reasonable expectation are not persuasive.

For the reasons set forth above and those previously enumerated, the rejection of these claims is maintained.

3. Claims 7, 10, 12 – 17, and 19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sanberg (1996. Soc. Neurosci. Abstr. 22(1-3):578, abstract 232.9) in view of Weiss (U.S. Patent 5,851,832) and Uchida (1995. Exp. Neurol 132:194-208).

This rejection stands for the reasons above and those previously made of record. Applicant did not traverse the examiner's determination that the reference by Uchida renders obvious the limitations drawn to sterility, recited in these claims. Rather applicant argues that the reasons why these claims are non-obvious over the cited art are the same reasons the other claims are non-obvious over the cited art, namely that the art does not lead one of ordinary skill to the number of cells to be administered and does not provide a reasonable expectation of success. For the reasons set forth in the previous rejection, these arguments are not persuasive. Therefore the present rejection stands for at least the same reasons.

Conclusion

4. No claim is allowed.

5. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Snable U.S. Patent 6,162,428, issued 19 December 2000, filed 12 February 1997. Similar to the reference by Sanberg cited above, the patent teaches administration of hNT cells to rats for treatment of stroke; see for example column 5 line 25 – column 11 line 65. While the reference is "by another", it does not explicitly teach administration to humans with stroke and does not specifically indicate that at least 6 million cells should be used. Rather the reference teaches 40,000 cells are optimal when administered to rats (column 11 final paragraph).

6. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANIEL KOLKER whose telephone number is (571)272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
February 3, 2009